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Chromosome 18 Translocation (18;21) (p11.1;p11.1) Associated With Psychosis in One Family

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In the course of recruiting families with 2 schizophrenic siblings for genome screening and linkage studies, a family was found with mental retardation, schizophrenia, and/or other related psychotic illnesses in individuals who also had an unbalanced or balanced translocation between chromosomes 21–18 [t(18;21) (p11.1;p11.1)]. The pericentric region of chromosome 18 has already been noted as a possible location of a gene for bipolar psychosis. The family described here provides further evidence that this region should be examined for a candidate psychosis gene. © 1996 Wiley-Liss, Inc.

KEY WORDS: schizophrenia, mental retardation, translocation, linkage, chromosome

INTRODUCTION

The occurrence of chromosome translocations in families also afflicted with an inherited illness can aid in the search for a genomic location of genes for that illness [reviewed in Bassett, 1992]. While the general region is narrowed by linkage to polymorphic markers, it is often too large to consider straight sequencing without having a more exact clue to the gene's location. Translocation breakpoints can then become candidates.

Berretinni et al. [1994] were the first to report (using nonparametric analyses) a linkage of bipolar disorder to a region of chromosome 18p11. Other research groups either found positive evidence for linkage spread over a wide area (40 cM) only partially overlapping with the original observation [e.g., Stine et al., 1995], failed to confirm any linkage [Pauls et al., 1995], or else found another independent region on chromosome 18 that is linked [Freimer et al., 1996]. Equivocal results were reported for this region in 32 families with schizophrenia by our own research group [DeLisi et al., 1995]. Since lod scores in the latter study were negative, we concluded that the findings were not strong enough to pursue this region further. Furthermore, none of the other above studies obtained a lod score with bipolar disorder that would be considered acceptable to confirm linkage by the standards recently published by Lander and Kruglyak [1995].

Despite the lack of clear evidence for linkage of any psychosis to chromosome 18 and the controversial nature of this linkage, the following observations of a chromosome 18 translocation in one family could be of interest.

SUBJECTS AND METHODS

Families are being recruited from throughout the USA in which at least 2 siblings have been diagnosed with schizophrenia for genome screening in an attempt to find a major gene locus linked to psychosis. In response to an advertisement for such families, an informant from the following family wrote to one of the investigators (L.E.D.) volunteering to participate in these genetic studies. A pedigree and structured family history were obtained, using procedures previously established [DeLisi et al., 1987]. Interviews of all available family members were performed, using the Diagnostic Interview for Genetic Studies (DIGS) [Nurnberger et al., 1994], and relevant medical records were obtained. A Structured Interview for Schizotypy (SIS, developed by K.S. Kendler), as modified by the NIMH Genetics Initiative Schizophrenia Genetic Linkage Sites (11/91)[Nurnberger et al., 1994], was used to determine schizophrenia spectrum personality traits. Diagnoses were made by consensus of two independent diagnosticians (L.E.D., P.P.) according to DSM-III-R [APA, 1987] criteria without knowledge of the cytogenetic results (Fig. 1).

Peripheral blood was sent to The Genetics Center, Inc., in Smithtown, NY (by J.W.) for karyotyping, because one family member informed the researchers that a physician previously "found some genetic abnormality of their chromosomes," although there was no history of any specific diagnosed genetic disorder in this family, and the primary diagnosis given by the physician for the 2 siblings was schizophrenia.

High-resolution G-banding was thus performed. A minimum of 20 cells was analyzed, and 3–4 cells were

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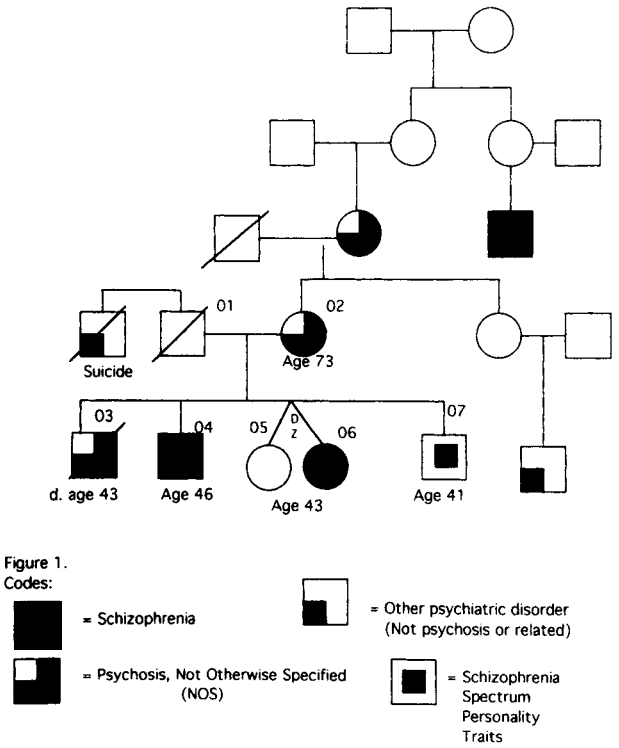

Fig. 1. Family pedigree with DSM-III-R diagnoses.

karyotyped for each of the 4 individuals studied (Fig. 2): the mother (#02), one daughter (#06), and 2 sons (#04 and #07). The daughter (#05), who was reported to be well, was unavailable. An in situ hybridization study (by J.W.), using a digoxigenin-labelled alpha-satellite probe for chromosome 18 and an enzymatic detection system (Oncor, Gaithersburg, Maryland), was performed.

CASE REPORTS

The mother (#02) is a 73-year-old widowed housewife. On karyotyping, all cells examined showed a balanced translocation between chromosomes 18–21. Even with high-resolution banding studies (750-band-level), breakpoints could not specifically be identified. Past history included a DSM-III-R diagnosis of Psychosis, not otherwise specified, consisting of two episodes of atypical paranoid psychoses, each lasting a few months at a time and resolving with neuroleptic medication given by a private outpatient psychiatrist. The first episode occurred when she was 51, and the second, 2 years prior to our interview. She had recovered at the present evaluation, was not on medication, and had no axis II diagnoses.

One of the sons, #04, is a 46-year-old supermarket worker. His karyotype showed the same balanced translocation between chromosome 18–21 in all cells examined. On review of medical records, information from his family, and a structured interview, he was diagnosed with chronic DSM-III-R schizophrenia, paranoid type. His symptoms included visual (not auditory) hallucinations, with multiple paranoid thoughts. His illness onset was at age 14; however, he managed to graduate high school in an honors program and, despite his illness, he served in the US Navy for 4 years. He had only one short hospitalization several years prior to the present evaluation for schizophrenia, but the records were not available. He has been medicated continually with neuroleptics to the present and was not psychotic at the interview.

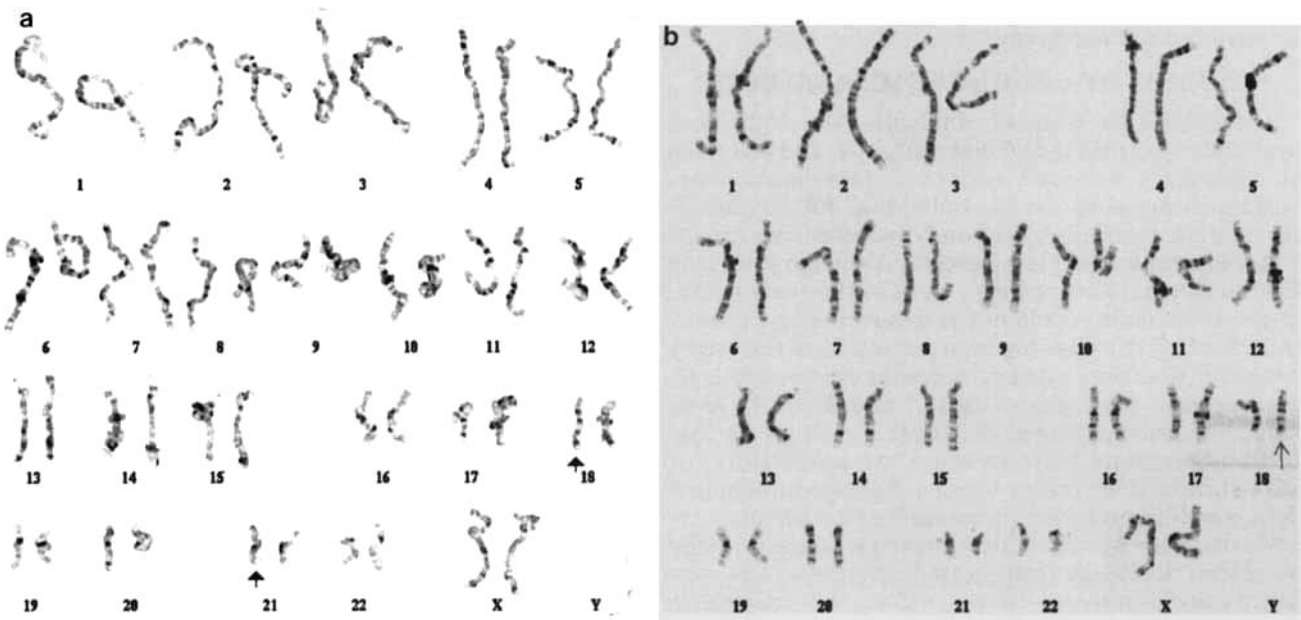

Fig. 2. **a**: Karyotype of individual #02, mother: balanced translocation between chromosomes 21p and 18p is illustrated, 46,XX,t(18;21) (p11.1;p11.1). **b**: Karyotype of individual #07, daughter: unbalanced translocation is illustrated, 46,XX,−18,+der18, t(18;21) (p11.1;p11.1)mat.

The daughter, #06, is 43 years old, unemployed, living with her mother (#02), and unable to care for herself. In all cells examined from this patient, a normal chromosome 18 was replaced by an abnormal 18 which had been derived from a reciprocal translocation between chromosome 18–21. Her unbalanced chromosome complement, which involved the loss of a portion of a chromosome 18 short arm, would have resulted from an adjacent-1 segregation during meiosis in her mother, who is the carrier of the balanced translocation.

Based on interview, family information, and medical records, she was diagnosed with DSM-III-R chronic schizophrenia, disorganized type, with mild mental retardation. Her illness was characterized by frequent auditory hallucinations, loud verbal outbursts, paranoid ideation, thought and language disorganization, and multiple negative symptoms. Illness onset was approximately at age 18, and positive symptoms appeared to partially respond to conventional neuroleptics. She has had two hospitalizations lasting several months each. She is described as having a severe speech impediment and several developmental physical anomalies, such as premature aging, and abnormal jaw, facial features, and arms.

Her brother, #07, is 41 years old, twice married, and employed as an accountant In all cells examined, his karyotype showed a balanced tranlocation of chromosomes 18 and 21, identical to that of his mother and brother.

On structured psychiatric interview, he displayed a few traits characteristic of paranoid and other schizophrenia-spectrum personality disorders, but not sufficient for DSM-III-R diagnostic criteria. He displayed expectation of trickery or harm by others, reluctance to confide in others, a tendency to be easily slighted, lack of strong emotions, and excessive social anxiety, and he refused a second interview after becoming suspicious of the examiner.

SUMMARY OF CHROMOSOME ANALYSES

High-resolution G-band analysis (700–750 band level) indicated that individuals #02, #04, and #07 have an apparently balanced reciprocal translocation between a chromosome 18–21. Individual #06 has inherited only the translocated 18 and, therefore, has an unbalanced chromosome complement. Although it is clear that the breaks occurred very close to the centromere, precise breakpoints could not be determined cytogenetically, leaving two possible interpretations of the origin of the translocation. Either the breaks occurred in both chromosomes' short arms (18p11.1 and 21p11.1), or in both chromosomes' long arms (18q11.1 or 21q11.1) (Fig. 3). To differentiate between these two possibilities, in situ hybridization studies using a digoxigenin-labelled alpha-satellite probe for chromosome 18 with an enzymatic detection system (Oncor) were performed. It was found that the longer translocated chromosome 21 contained the chromosome 18 centromere, indicating that the chromosome breaks that led to the formation of this translocation occurred in the short arms of chromosome 18 and chromosome 21 (Fig. 4). Thus, the karyotype must be interpreted as 46,XX or XY,t(18;21)(p11.1;p11.1). No other chromosomal abnormalities, such as X-chromosome aneuploidies, were found in this family.

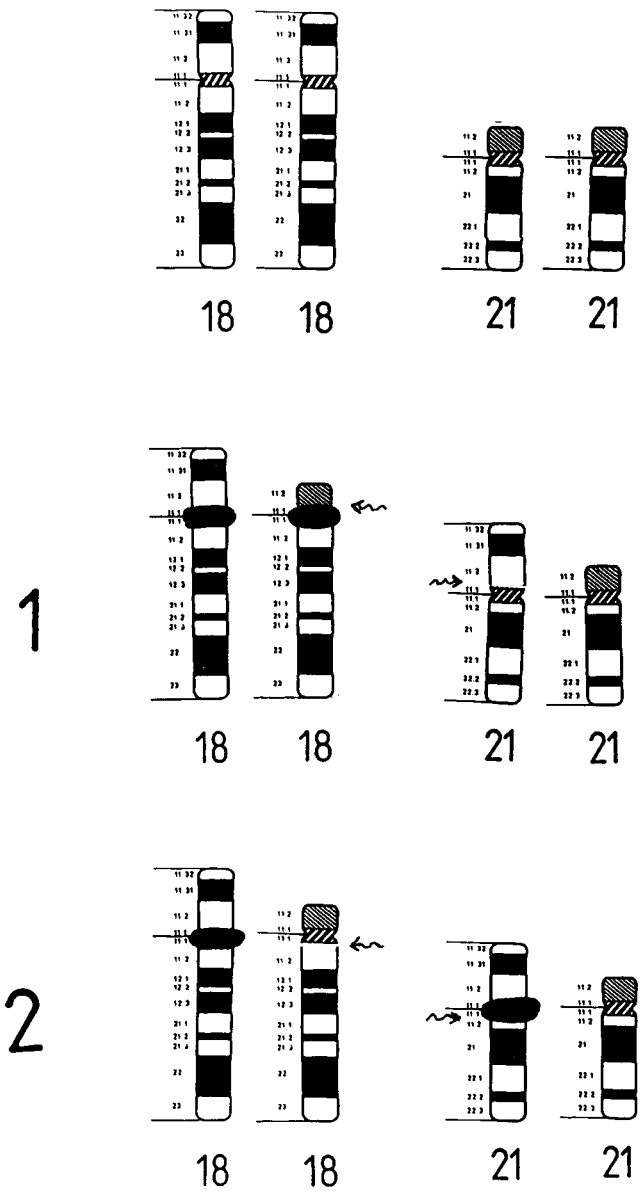

Fig. 3. Diagram showing normal chromosomes 18 and 21 (**top**) and the two possible (**1** and **2**) cytogenetic interpretations of the breakpoints (⇝) involved in the translocation, and the positions of the chromosome 18 alpha-satellite probe hybridization sites (represented as ⇝) that would be expected, depending on the interpretation. 1: Short arm location. 2: Long arm location.

DISCUSSION

Individuals with deletions of the chromosome 18 short arm tend to have a characteristic physical appearance, with craniofacial dysmorphism, broad, short hands and limbs, and other features, such as webbed neck, suggestive of Turner syndrome. Mental retardation is usually present and varies from mild to severe [Rethore, 1977]. Behavioral syndromes such as autism,

Fig. 4. Metaphase of a balanced translocation carrier showing that the chromosome 18 alpha-satellite probe hybridizes to the normal chromosome 18 and to the longer translocated chromosome (t(18)). Therefore, the breaks occurred in the short arms of both chromosomes.

schizophrenia, agitation, and excessive fear of strangers have also been previously reported in isolated cases [Grouchy et al., 1963; Grouchy, 1969; Rethore, 1977; Schinzel et al., 1974; Uchida, 1965]. No known syndromes have been published for breakpoints on chromosome 21p.

In the family described here, all individuals with the 18/21 translocation demonstrated psychotic episodes and/or some schizophrenia-spectrum traits. The one individual with an unbalanced translocation resulting in deletion of the chromosome 18 short arm was the most severely ill. Unfortunately, one daughter who according to other family members is well, was not available to determine whether or not she also inherited the translocation. Thus, we cannot say for certain that this family provides evidence of an association of schizophrenia and schizophrenia-spectrum disorders with chromosome 18p.

However, the 2 individuals diagnosed with schizophrenia, in general, displayed a typical spectrum of symptoms, course, and response to medication that can be seen in the majority of patients with this diagnosis, given that the clinical manifestations are extremely heterogenous. Thus, the cases described here are not atypical.

We are not suggesting that this translocation itself could be causing the symptoms. Rather, it is possible that the breakpoint on chromosome 18 for this translocation, which has been identified at 18p11.1, may indicate a candidate region for a psychosis gene. Families with such a translocation can often be useful in then mapping the gene involved. Cell lines from this family are available and may provide further information for localizing the gene sequence involved.

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